REMARKS

The Office Action of June 23, 2010, has been carefully studied. Claims 1-17 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al., EP 1082963 and Snow et al., WO 94/13327, in view of Nogusa et al., US 5,688,931.

This rejection is respectfully traversed.

Tamura relates to a conjugate of hyaluronic acid, a derivative thereof, a salt thereof, and a therapeutic agent for joint disease, which can retain the therapeutic agent in joint cavities (see Abstract). As described in paragraph [0014] of the present specification, WO 99/59603, which corresponds to Tamura, Tamura states that the conjugation between the hyaluronic acid and the drug through the spacer is relatively strong, making it difficult to administer a drug like methotrexate, which cannot exert a beneficial effect unless it is released from the conjugate. Note at paragraph [0019], the conjugate remains in the joint cavity for a long period of time after being administered. Tamura specifically states that the antirheumatic agent/HA conjugate exhibits MMP inhibition even in the conjugate form [paragraph 0018].

The components of the conjugate are said to exhibit their own efficacies to produce the desired synergism as they can show their activities **without being dissociated or decomposed** (paragraph [0149], emphasis added). That is, Tamura discloses a conjugate which is not dissociated at the point of administration.

It should be noted that Tamura discloses conjugates of a great many matrix metalloprotease inhibitors, only one of which is methotrexate. While it may be possible that some of the MMP's disclosed in Tamura can be effective while still conjugated to hyaluronic acid or a derivative thereof, this is not the case for methotrexate. Submitted herewith is a copy of Homma et al., *Bioorganic & Medicinal Chemistry*, **17**:4647-4656, 2009, published long after the filing date of the present application, that states that methotrexate does not exhibit any physiological effects when conjugated. This is described in the chemical structures of Conjugates 1 and 2 shown on page 4648, and the data on these conjugates in Table 1 on page 4650. While Tamura discloses conjugates of hyaluronic acid with an MMP, there are no working examples in Tamura of a methotrexate conjugate.

Snow relates to diagnostic imaging of cancer and radiological treatment of cancer by means of a tumor targeted sequential delivery system (Field of the Invention). This has nothing to do with providing a methotrexate conjugate that delivers methotrexate to a join over a period of time as the conjugate dissociates, as the Snow conjugate is used for an entirely different

purpose from that of the presently claimed conjugate, *i.e.*, treatment of joint disease by delivery of methotrexate to a joint. Additionally Snow fails to teach a beneficial effect of either hyaluronic acid or methotrexate, in particular, on joint diseases. Therefore, one skilled in the art would have no motivation to combine Tamura with Snow.

Nogusa relates to a polysaccharide derivative which has a property of accumulating in large amounts at a tumor (see column 2, lines 4-8). Snow is relevant to Tamura but not to the conjugate claimed herein. Additionally, in Nogusa, the polysaccharide is considered to be merely useful as a carrier in treating a tumor, whereas the presently claimed conjugate uses hyaluronic acid as an active ingredient. Therefore, one skilled in the art would have no motivation to combine Tamura with Negus.

Furthermore, the presently claimed conjugate possesses many advantages over the prior art citations, as described in the previously filed response (please refer to page 20, line 1 to page 21, line 9 of the previous response), as follows:

> The claimed conjugate has many advantages over the prior art. First, as described in paragraph [0044] in the present specification, in the treatment of joint disease, the conjugate has both the pain-eliminating effect of hyaluronic acid (HA) as well as the synovitis-alleviating effect of methotrexate (MTX).
>
> Further, as described in paragraph [0045] of the present specification, when administered to the knee joint of OA or RA patients, the conjugate accumulates in synovial tissue and is gradually incorporated into synovial cells, where it

> releases MTX to exert a persistent synovitis-suppressing effect, resolving a problem that MTX rapidly disappears from a joint cavity, as described in paragraph [0010]. The 'HA in the conjugate enables the conjugate to accumulate in synovial tissue, and thus functions as a drug delivery system for MTX. This makes it possible to administer a greatly reduced dose of MTX compared to that for oral administration thereof, and can thereby eliminate problems of systemic side effects, which may occur with oral administration of MTX. Further, the HA and MTX can exert pharmacological effects that are different from each compound alone, and a synergistic beneficial effect is obtained. In the working examples, particularly as shown in Figures 2 and 3, it is shown that the synergistic effect f the conjugate is beyond the expectations of those skilled in the art based on the effects of MTX or Ha alone.

None of the cited references would lead one skilled in the art to expect these properties from a hyaluronic acid-methotrexate conjugate. In particular, Tamura teaches the enhanced retention of and MMP inhibitor by strong conjugation of the inhibitor to hyaluronic acid. It is respectfully submitted that the enclosed article from ***Bioorganic and Medicinal Chemistry*** ***s***hows the advantageous effect of the herein claimed conjugate over those of the prior art. Specifically, although Conjugates 1 and 2 have a similar linker to those of Tamura, these conjugates were unable to inhibit proliferation of synovial fibroblasts. Conjugates 2 and 4, which are within the scope of the present claims, did exhibit such inhibition.

With respect to claims 10 and 11, since the claimed conjugate is novel and unobvious, the intermediate of the conjugate (claim 10) and the process for producing the conjugate (claim 11) should also be patentable. It

should be noted that claim 10 does not include the compounds disclosed in Snow, compound 1 in Scheme 4 at page 42.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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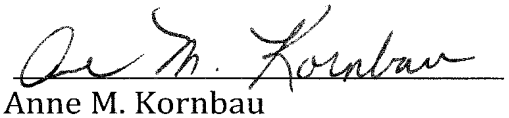
By 
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